REMARKS

A Petition for Extension of Time is being concurrently filed with this Amendment. Thus, this Amendment is being timely filed.

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

Status of the Claims and Support for Amendments

In the present Amendment, claims 1 and 3 have been amended and claims 7-10 have been added. Thus, claims 1 and 3-10 are pending in the present application.

No new matter has been added by way of these amendments because each amendment is supported by the present specification. For example, the limitation regarding the molecular weight of the drug is supported by the specification at page 9, second full paragraph. The remaining amendments to the claims are made in order to clarify the claimed invention. The limitations in new independent claim 7, which are not present in the other independent claims, are supported in the specification as follows: "an aqueous solution of said drug is dropwise added" (see the paragraph bridging pages 9 and 10); and "aqueous solution being added dropwise causes swelling of the crosslinked hydrogel" (see page10, lines 17-21). Support for new claims 8-10 can be found in the second full paragraph on page 9 of the specification.

Applicants are in no way conceding any limitations with respect to the interpretation of the claims under the Doctrine of Equivalents.

Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicant respectfully requests that the Examiner withdraw all rejections and allow the currently pending claims.

Substance of the Interview

Applicants thank the Examiner for his time, helpfulness and courtesies extended to Applicants' representative during the Interview of May 6, 2010. The assistance of the Examiner in advancing prosecution of the present application is greatly appreciated. In compliance with M.P.E.P. § 713.04, Applicants submit the following remarks.

The Interview Summary form amply summarizes the discussions at the Interview. Various ways of addressing the prior art rejections were discussed, and suggestions were discussed that may be drafted to cover particular aspects of the invention as not described by the prior art. Applicants have adopted the Examiner's suggestion to change "maintained" to "immobilized."

Rejection Under 35 U.S.C. § 102(b)

The Examiner has maintained the rejection of claims 1, 3, 5 and 6 under 35 U.S.C. § 102(b) as being anticipated by **Tabata et al.** (*Advanced Drug Delivery Reviews*, Vol. 31, pp. 287-301 (1998)). Applicant respectfully traverses, and reconsideration and withdrawal of this rejection is respectfully requested.

There were previously two independent claims, which are claims 1 and 3, and a new independent claim 7 has been added. Claim 1 is drawn to a sustained-release preparation and

claim 3 is drawn to a method of sustained release of a drug *in vivo*. Claim 7 includes all the limitations of claim 1 and further contains certain product-by-process limitations.

The Examiner asserts that Tabata discloses all claimed features. With regard to the claimed "concentration gradient being higher at said surface than in other parts of said hydrogel," the Examiner concludes (after a thorough discussion) that:

> The limitation of a concentration gradient of the drug in the hydrogel, the concentration gradient being higher at the surface than in other parts of the hydrogel is anticipated by the release of drug from the gelatin hydrogel as a result of its biodegradation, as taught by Tabata (Abstract). Since the protein drug is applied on the surface of the gelatin hydrogel, the concentration of the drug will intrinsically be higher on the surface. (page 5, first partial paragraph of Office Action)

Applicants respectfully submit that to support an anticipation rejection based upon inherency, an Examiner must provide factual and technical grounds establishing that the inherent feature ***necessarily*** flows from the teachings of the prior art. See *Ex parte Levy* 17 USPQ2d 1461 (BOPAI 1990); see also *In re Oelrich*, 212 USPQ 323 (CCPA 1981) holding that inherency ***must*** flow as a necessary conclusion from the prior art, not simply a possible one. The Examiner appears to be taking "Official Notice" of several facts which are unsupported by documentary evidence. MPEP 2144.03 gives instructions on when Official Notice unsupported by documentary evidence is appropriate. MPEP 2144.03 states:

> Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known.

The Examiner appears to take Official Notice of the fact that the concentration gradient would be higher at the surface than in other parts of the hydrogel in view of the fact that the drug will release from the gelatin hydrogel as a result of its biodegradation. It is unclear to Applicant

what basis the Examiner has for making this statement. Applicant respectfully challenges this first assertion by the Examiner. Applicant requests that the Examiner provides documentary evidence to support the assertion that the concentration gradient would be higher at the surface than in other parts of the hydrogel in view of the fact that the drug will release from the gelatin hydrogel as a result of its biodegradation.

Furthermore, if it is the Examiner's position that a *prima facie* case of anticipation is present in view of the fact that the concentration gradient would be **inherent** in the hydrogel of Tabata et al., Applicant respectfully disagrees. In order for the Examiner to set forth a *prima facie case*, there must be sufficient evidence in the cited reference to assert that the missing feature of the claimed invention is actually in the product of the prior art. To support an anticipation rejection based upon inherency, an Examiner must provide factual and technical grounds establishing that the inherent feature necessarily flows from the teachings of the prior art. See *Ex parte Levy* 17 USPQ2d 1461 (BOPAI 1990); see also *In re Oelrich*, 212 USPQ 323 (CCPA 1981) holding that inherency must flow as a necessary conclusion from the prior art, not simply a possible one. Here, we do not believe that the cited reference provides any disclosure which would make one skilled in the art believe that the concentration gradient would necessarily be **inherent** in the hydrogel of Tabata et al.

Although it is unclear to Applicant what the basis for the Examiner's belief is, Applicant guesses that the Examiner believes that the discussion of "sorption" of the protein relates to surface adsorption. However, this is not the case. For example, the Examiner's attention is drawn to Section 3.2 of Tabata et al. titled "Interaction of protein with gelatin hydrogels" beginning on page 292. The Examiner will note that Tabata et al. state: "the interaction of protein with gelatin

results in protein sorption to the gelatin hydrogel." At the top of the second column on page 292, Tabata et al. state that the bFGF protein molecules "***freely diffuse into the interior*** of the hydrogels." (Emphasis added). Applicant respectfully submits that express statement in Tabata et al that the bFGF molecules freely diffuse into the interior of the hydrogels is a true statement that is also supported by scientific principles.

It is submitted that the Examiner is not in a position to question the truth of the express statements made in Tabata without a strong scientific basis. A skilled artisan would not reasonably conclude that protein molecules which freely diffuse into the interior of a hydrogel would have a concentration gradient with a higher concentration at the surface. The Examiner appears to take Official Notice of the fact that the concentration of the drug will intrinsically be higher on the surface, since the protein drug is applied on the surface of the gelatin hydrogel. Again, Applicant respectfully challenges this assertion by the Examiner. In general, gelatin and collagen hydrogels have higher affinity with substances of low molecular weight than of higher molecular weight. When an aqueous solution of a drug with a higher molecular weight, such as bFGF (17 kD) disclosed in Tabata et al, is applied dropwise to a hydrogel, the gel will swell with the solution and thereafter the drug will be gradually bound to the hydrogel and immobilized. This means that when an aqueous solution containing a drug with higher molecular weight is added dropwise to the hydrogel, a concentration gradient will not be formed within the gel.

Although Applicant's examples in the present specification are not limiting of the invention, the Examiner will note that the examples in the present specification describe a method of forming the sustained-release preparation which is very different from the method discussed in Tabata et al. Also, the molecular weight of the drugs has now been limited and the

molecular weight has an effect on diffusion characteristics as discussed above. As such, it is submitted that there is no longer any basis for the Examiner's assertion that *prima facie* case of anticipation is present in view of the fact that the concentration gradient would be **inherent** in the hydrogel of Tabata et al.

To summarize, Tabata et al discloses that protein drug complexed with gelatin hydrogel is released as a result of its biodegradation, but does not at all teach or suggest "concentration gradient" of the protein.

The Examiner apparently is also speculating that the concentration gradient will be generated when the hydrogel is biodegraded or when a protein is applied to the hydrogel. However, as discussed previously, when a pharmaceutical composition is administered to a patient, the composition is no longer "sterile" as required by the claims because of the presence of living cells that are necessarily present when the composition comes into contact with a human, such as when it is implanted or swallowed. Thus, even if such a concentration gradient is formed during degradation (which applicants do not concede), inherent anticipation does not exist.

As such, clear patentable distinctions exist between the present invention and the teachings of Tabata et al. and a *prima facie* case of anticipation cannot be said to exist.

When a substance with a molecular weight of about 10,000 or less is added dropwise to a hydrogel, the drug will immediately bind to the hydrogel at or near the point of addition and thus cannot be dispersed homogeneously within the gel thus forming a concentration gradient of the drug within the gel. This is clearly described in the general description and Examples of the present application.

In view of the above explanation, it is submitted that the rejection of the previous version of the claims for inherent anticipation should be withdrawn. Although applicants assert that a *prima facie* case of inherent anticipation has not been established, the independent claims have been further amended to indicate that the molecular weight of the drug is about 10,000 or less. In contrast, the molecular weight of the bFGF disclosed in Tabata et al is 17 kD; which is much higher than the upper limit of about 10,000 as recited in the currently pending claims.

If the Examiner persists in asserting that the concentration of the drug in Tabata will intrinsically be higher on the surface, since the protein drug is applied on the surface of the gelatin hydrogel, the Examiner is requested to provide documentary evidence to support such assertion. In any event, the inclusion of the about 10,000 molecular weight limitation into the claims should resolve any inherent anticipation issues that might exist.

Rejection Under 35 USC 103(a)

Claim 4 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over **Tabata et al.** in view of **Ueda et al. '574** (US 4,749,574).

With respect to the obviousness rejections, a retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in a particular claimed combination. *See In re Newell*, 891 F.2d 899, 901, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989). Further, *In re Spormann,* 150 USPQ 449 (CCPA 1966), teaches that arguments based on inherent properties cannot stand when there is no supporting teaching in the prior art. *Spormann* instructs us that inherency and obviousness are distinct concepts.

In *Spormann*, the invention related to a process of producing alkali metal sulfites from alkali metal hydroxides and/or carbonates by spraying the latter, in aqueous solution, into a dry gas containing sulfur dioxide. The temperature and humidity of the gas were set to vaporize the

water immediately without producing much sulfate. The chemical reaction in the invention was old, but the conducting of the chemical reaction by spraying an alkali metal compound into the gas stream to cause all the water present to be vaporized immediately was not specifically shown in the prior art. The claimed invention was rejected as being obvious in view of the reference Frederich et al. and other secondary references. Frederich et al. taught a process for making sodium sulfites where a raw material such as sodium hydroxide or sodium carbonate was passed in a solid, powdered form. The solid material carried a specific amount of water throughout the entire process.

On appeal, the CCPA held that none of the cited references suggested the reduction of sulfate when the reactant gas contained large amounts of oxygen. In addition the CCPA stated that:

> the board apparently thought that the minimizing of sulfate production would be *inherent* in the process of Frederich et al.... As we pointed out in *In re Adams*..., the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.

Based on this reasoning, the CCPA reversed the obviousness rejection.

In response, Applicant respectfully submits that Tabata et al., either taken alone, or in combination with Ueda et al., fail to teach or fairly suggest all of the features of the presently claimed sustained release preparation of claim 1 or the method of claim 3. For example, as discussed above, it is submitted that Tabata et al. fail to teach or suggest a concentration gradient of the drug. And, even if such a concentration gradient inherently existed when the composition is degraded, it would not be obvious to make a sterile composition based on something that might be transitorily inherent in a non-sterilc composition in the prior art.

In addition, the Examiner cites Ueda et al. in order to cure deficiencies in Tabata et al. with respect to present claim 4. However, Ueda et al. fail to cure the deficiencies of Tabata et al. that are discussed above and therefore even if Ueda et al is combined with Tabata et al a *prima facie* case of obviousness does not exist.

Information Disclosure Statement

Applicants note that an Information Disclosure Statement was filed on January 27, 2010, which is after issuance of the current Office Action. Consideration of the cited materials and a returned, initialed copy of the SB/08 form are respectfully requested.

Conclusion

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eugene T. Perez, Reg. No. 48,501, at the telephone number below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____
Gerald M. Murphy, Jr.
Registration No.: 28,977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road, Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant